REMARKS

The Office Action mailed December 30, 2005, has been carefully reviewed.

Claim 33 has been amended, claim 47 canceled, and claims 53-54 added.

Claims 24 – 32 stand withdrawn as deemed to be allegedly directed to a non-elected invention; claims 1-23, 35, 36, and 42 remain canceled.

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failure to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement.

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

Claims 33-34, 37 – 40, 43-49, and 51 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 33, 34, 37, and 46-51 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Valenta et al. (WO 99/16467) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 33, 49, and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659) in view of Hem et al.

Claims 33, 38, and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

The claims as amended herein are fully supported by the application as originally filed. No new matter has been added. Reconsideration and allowance of the present application are respectfully requested in view of the foregoing amendments and the following additional remarks which have addressed all the grounds for objection or rejection or otherwise have rendered them moot.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failure to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that

independent claim 33 recites grass pollen allergens which is incongruous with the tree allergens of alder, hazel and birch, specifically claimed in previously presented claim 33-dependent claim 47.

To obviate this ground for rejection, Applicants have incorporated the subject matter of previously presented claim 47 into claim 33, which as now amended, is directed to allergens derived from the naturally occurring allergens of alder, hazel and birch. The ground for rejection now moot, it is respectfully requested that it be withdrawn.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement for allegedly adding new matter. According to the Examiner, the recitation in amended claim 33 that the specific IgE binding to the administered derivative is 50% or less compared with IgE binding to the naturally occurring allergen is not adequately supported by the specification. Basically, it is the Examiner's contention that "50% or less IgE binding" is not scientifically equivalent to "50% or less allergenic activity" because the specification had recited the latter and not the former. Applicants respectfully disagree and traverse as follows.

The basis of the Examiner's rejection is his assertion that the "binding to preexisting IgE antibodies and the ability to elicit new IgE antibody production are distinct properties." The Examiner understands the phrase "allergenic activity" to mean the capacity to "induce an IgE response." The Examiner thus equates "eliciting new IgE antibody production" with "inducing IgE response."

On page 4, paragraph 3, Applicants categorically stated that "the allergenic activity is determined by determining the IgE antibodies which are induced in a test animal." The Applicants went on to describe the basophil histamine release assay as a preferred in vitro test for determining allergenic activity. By definition the basophil histamine release assay measures IgE antibodies which are induced in a test animal because one skilled in the art knows to use scientific methods to control (by using a test sample and a control sample) for the so called pre-existing IgE binding. Applicants do not believe that the Examiner is insisting that the specification should have been belabored by such standard protocols as teaching a scientist how to do a controlled experiment. And Applicants believe that by carrying out such controlled experiments, the specification not only adequately describes, but enables the determination of IgE antibodies induced as a result of a given allergen. The

Examiner is further asked to bear in mind that applicants used the phrase "50% or less" and believe that that 0 – 50% margin obviates any distinction in the Examiner's mind as to patentability and scientific exactitudes between the complained of phrases.

In view of the foregoing, Applicants believe that this ground for rejection has been obviated and it is respectfully requested that it be withdrawn.

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement because the specification does not provide enablement "for a method of treating or preventing all IgE-mediated disorders by administering derivatives of grass pollen allergens. The current amendment to claim 33 has obviated this ground for rejection by directing claim 33 to the treatment of IgE-mediated allergic disorders induced as a result of exposure to the major allergens of alder, hazel and birch.

Further the Examiner asserts that the claim preamble does not limit the IgE-mediated disorders to those that involve only grass-pollen allergen specific IgE-antibodies. Again, the amendment to claim 33 has obviated this ground for rejection. Suffice it to mention that the preamble of claim 33 was directed to an" IgE-mediated allergic disorders" and not "IgE-mediated disorders" and went on to particularly enumerate the specific group of allergens involved.

Further, the Examiner asserts that the specification "does not appear to define the term prevent." Applicants contend that they are not obligated to ordinarily define words that should be plainly and ordinarily understood. According to the Examiner, "IgE-mediated reaction cannot be prevented because it has already occurred." Applicants respectfully ask the Examiner to limit his construction of the claims to what the plain and ordinary language of the claims. The claims are directed to the treatment or prevention of IgE-mediated allergic disorders and not to the treatment of "IgE-mediated reactions." Moreover, IgE-mediated allergic reaction can be prevented where the treating regimen constitutes the sensitizing exposure. There is no reason why the pharmaceutical composition of this invention cannot be administered to people at the risk of exposure without first waiting for them to be exposed. In that sense at least, the immunotherapeutic agents of this invention can have a preventative effect. For that reason at least, Applicants respectfully ask the Examiner to withdraw this ground for rejection.

The Examiner further asserts that claim 52, to the extent that it is dependent on claim 33, is without support in the sense that trimers of Bet v 1 do not show a dimunition in specific IgE binding although said trimer, when administered into an experimental animal, do not elicit a significant IgE response that was directed to Bet v1. According to the Examiner, therefore, Bet v1 trimer has the functional property of reduced allergenic activity but does not have the recited property of a diminished capacity to bind pre-existing allergen specific IgE as compared to the wildtype allergen. In making this assertion, the Examiner does not appear to have taken into consideration the effect of the presence of IgE-blocking antibodies in the asserted distinction between in vivo IgE-binding and induction of allergic reaction. Taking into proper consideration, the presence of IgE-blocking antibodies leaves the Examiner's contention without merit and it is respectfully requested that this ground for rejection be withdrawn.

For that matter, the Examiner further asserts that the specification does not appear to teach what changes to be made to naturally occurring allergens to make the derivates that satisfy the recited functional criteria, and the teachings of the art indicate that the structure of the material obtained as an immunotherapeutic agent at the conclusion of the screening protocol cannot be predicted. Indeed, the utility of the present invention lies in obviating the need for experimentally intensive predicted structural characterization of putative immunotherapeutic agents.

The methodology of the present invention is based on the theory that allergen-specific IgG antibodies, termed blocking antibodies, can antagonize the cascade of allergic inflammation resulting from allergen recognition by IgE antibodies. The instant invention is based on the rationale that blocking antibodies inhibit allergen-induced release of inflammatory mediators from basophils and mast cells as well as IgE-facilitated allergen presentation to T cells, thus leading to suppression of T cell activation. Furthermore, the development of blocking antibodies is associated with reduced boosts of allergen-specific IgE production in patients receiving allergen-specific immunotherapy of the present invention. Thus blocking antibodies have protective activity by inhibiting immediate as well as late inflammatory responses and long-term ameliorating activity on the allergic immune response by antagonizing the underlying IgE production. Induction of blocking antibodies is thus an important mechanism underlying allergen-specific immunotherapy. See Specification pages 5 and 6.

As now distinctly claimed, a method of treatment using **derivatives** (not necessarily allergenic) capable of, **in vivo**, inducing IgG antibody production, while simultaneously

inhibiting the binding of and or decreasing the production of allergen-specific IgE against naturally occurring allergens, are the derivatives of the present invention.

The methodology of the instant invention is simple, elegant and very effective. It does not concern itself with structural characterization of the allergen, nor the experimentally intensive structural characterization of the allergenic derivative, but instead chooses such derivatives, of whatever structural configuration, derived by substitution, fragmentation or any other means in the art, that is capable of inducing sufficient IgG production in vivo, such that the binding of allergen-specific IgE to the naturally occurring allergen is substantially reduced, if not totally eliminated. While some experimentation is required, it is respectfully not undue when compared with epitopic mapping of putative immunotherapeutic agents.

Since the claims are now distinctly drawn to the use of derivatives that induce IgE-blocking antibody production, Applicants ask the Examiner to recognize that their method of treating allergic disorders is an elegant patentable departure from the experimentally intensive methodology of first typifying the epitopic domains of allergens and directing modifications thereto. Applicants recognize that reduction or elimination of IgE binding is the ultimate therapeutic goal in the treatment of allergic disorders and that the complex patho-physiologic mechanisms of allergic response presents many therapeutic targets. The instant invention, on the other hand, and especially as now distinctly claimed, concerns itself with treatment using derivatives simply and quite elegantly identified by their ability to elicit IgE-blocking antibody production *in a test animal.* Applicants respectfully ask that this ground for rejection be withdrawn for at least the fact that the screening of candidate immunotherapeutic agents of this invention do not involve undue experimentation.

Claims 33- 34, 37 – 41 and 43-52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner asserts that the three examples concerning the birch pollen allergen Bet v1 is insufficient to enable claims to the genus – namely derivatives of wild type allergens of alder, hazel and birch. Applicants respectfully disagree. The presented examples are to validate the inventors discovery that IgE-blocking antibodies do present a therapeutic handle for combating IgE-mediated allergic disorders. The Examples are not scope limiting, in the sense that the full scope of the invention can be practiced without undue experimentation. The written description requirement has been met in this case by disclosure of relevant identifying characteristics – namely that the candidate therapeutic agents of this invention are those which upon injection into an immunological model elicit both IgE-blocking antibodies

production and also have reduced allergenicity compared to wild-type allergens. This identifying characteristic, without more, has given possession to the Applicants, as at the filing date, of treatment methods using the results of the elegant in vivo screening methodology of the present invention.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 33-34, 37 – 40, 43-49, and 51 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659). The Examiner asserts that Vrtala et al., teach a method of treating allergy by administering derivatives of Bet v1 that induce the production of IgE-blocking antibodies and that are not bound by IgE antibodies that are specific for wildtype Bet v1. Applicants respectfully disagree and now traverse as follows.

First, the present application claims priority to European Patent Application 00128661.6 filed on December, 28, 2000. Applicants also note that the inventorship of the instant Application and the authorship of the asserted prior art are common and Applicants respectfully assert that Vrtala et al. is not a proper prior art reference.

But even at that, a § 102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. *Paperless Accounting, Inc. v. Bay Area Rapid Transist Sys.*, 804 F.2d 659, 231 USPQ 649 (Fed. Cir. 1986), cert. denied, 480 U.S. 933 (1987). Indeed, to anticipate, a publication "must show the same subject matter as that of the patent, and must be identical in all material respects." *Hupp v. Siroflex of America, Inc.*, 122 F.3d 1456, 43 USPQ2d 1887 (Fed. Cir. 1997).

The Vrtala publication is at best a mere experimental disclosure of certain aspects of the present invention and does not enablingly disclose the invention as claimed. Particularly, and as the Examiner correctly observed, the Vrtala reference had not enabled treatment of human IgE-mediated disorder. Claim 33 as amended has been limited to human patients and for that at least, there is no further basis for a § 102(b) rejection and it should therefore be withdrawn.

Additionally, Applicants respectfully ask the Examiner to consider that claim 33 and its dependent claim have a periodicity element which is essential to successful immunotherapy. The Vrtala reference merely administered monthly administration of the allergen derivatives in order to conceptually investigate the subject matter thereof. There was no attempt in the Vrtala reference to investigate optimal periodicity intervals for the allergen administration and although it may have made reference to monthly injection of allergens, the

Vrtala reference cannot reasonably be said to have sufficiently disclosed, to a patentably enabling detail, the periodicity element claimed in the invention and which is very vital to a successful immunotherapy. For that at least, there is again no further basis for retaining this § 102(b) rejection and Applicants respectfully ask that it be withdrawn.

Claims 33, 34, 37, and 46-51 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Valenta et al. (WO 99/16467) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659). Applicants respectfully disagree.

Again, to be anticipating, a prior art reference must disclose "each and every limitation of the claimed invention, ..., must be enabling, and must describe ... the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *In re Paulsen*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1672 (Fed. Cir. 1994).

The Examiner acknowledges that Valenta et al. WO 99/16467 had not disclosed the concept of blocking antibodies but insisted that it is inherent in the disclosure of Vrtala et al. Applicants however believe that neither Valenta et al. alone or in combination with Vrtala et al. can be said to have enablingly disclosed the periodicity element of claim 33 and its dependent claims. For that at least, there is no basis for this ground for rejection and it is respectfully requested that it be withdrawn.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 33, 49, and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659) in view of Hem et al.

Applicants respectfully disagree that there is sufficient motivation to make the asserted combination. Hem et al., on page 249 taught that the aluminum containing adjuvants have been used for vaccines like diphtheria vaccine. The present invention has to do with immunotherapeutic agents which is not the same as vaccines.

But assuming the combination can be made, the asserted combination cannot on the basis of the arguments presented above render obvious the claims of the present invention. Basically, the periodicity element of the present invention cannot be met by the asserted combination. Again, although Vrtala mentioned monthly injection of allergen derivatives, it had not sufficiently disclosed to one of skill in the art the periodicity of injections so critical to successful immunotherapy. Basically Vrtala taught a concept but had not reduced it to

practice and the concept taught by Vrtala did not render the periodicity element of the present invention obvious by any stretch.

For that at least, there is no basis for this rejection and Applicants respectfully ask that it be withdrawn.

Claims 33, 38, and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659). The Examiner's basis for this rejection is that determining the optimum or workable ranges in terms of time intervals between administrations of allergens involves only routine skill in the art. Applicants respectfully disagree.

Applicants understand that a simple and elegant screening procedure of this invention involves routine skill in the art and that is why Applicants believe that there are in possession of fragments of allergens which meets the two prong limitation of claim 33. But the Examiner may not avail himself of hindsight gained by reviewing the instant Application in order to mount objections and/or rejections thereto. Allergy vaccines may be administered once in a life time, once in a season, and so on, but there is nothing obvious about determining not only the relevant periodicity of administration but the exact dosages involved. All of that information are garnered through rigorous experimentation that warrant protection for the ingenuity in discovering first how to screen allergen derivatives as potential immunotherpaeutic agents, then how to administer those allergen derivatives to treat IgE mediated disorders; both the screening and the administration warranting patentable protection for their immense contribution to the advancement of the science of immunotherapy.

CONCLUSION

In view of the foregoing remarks, Applicants submit that there is no basis for applying the previous rejection to the pending claims and withdrawal of the rejections is respectfully

requested. The claims are believed to be in condition for allowance, and Applicant earnestly solicits from the Examiner early notification of allowability.

Should the Examiner have any questions or believe a personal or telephonic interview may be in order, she is invited to contact the undersigned at his earliest convenience.

Respectfully submitted,

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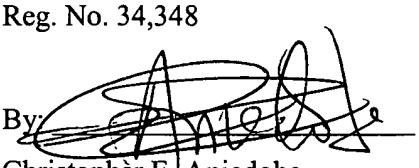
By: 

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